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Prevention of Malaria in Long-term Travelers

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TRAVELER ARRIVALS WORLDWIDE exceeded 800 million in 2005.¹ Today's mobile populations and global economies lead to extended stays for many travelers. For long-term travelers visiting malaria-endemic countries, recommendations for prevention have been difficult to standardize due to the diversity of long-term travelers and their itineraries, the variation in quality of and access to medical care, the limited data on malaria incidence in travelers overseas, and the lack of controlled studies on long-term safety and efficacy of antimalarial agents. Further complicating the recommendations are the evolution in the intensity of transmission and resistance patterns of the malaria parasites, the seasonality of transmission, and the wide range of international guidelines and travelers' beliefs and expectations.

EVIDENCE ACQUISITION

We searched the literature using MEDLINE via both OVID and PubMed for relevant studies and articles with a cutoff date of July 2006, using the search terms *long-term travel and malaria prevention*, *long-term malaria chemoprophylaxis*, and *insect repellent and malaria*. We obtained additional references from searching the bibliographies of the selected articles, from dissertations, and from the proceedings of relevant conferences on travel medicine. There were no language restrictions. We also systematically reviewed the following jour-

Context Long-term travelers, defined here as those traveling for periods of 6 months or longer, face particular challenges regarding malaria prevention. Current guidelines for malaria prevention primarily address prevention of *Plasmodium falciparum* infections in short-term travelers.

Objectives To examine the risk of malaria in long-term travelers, recent developments in personal protective measures, and the safety and tolerability of malaria chemoprophylaxis during long-term use and to consider prevention strategies including continuous chemoprophylaxis, stand-by emergency self-treatment, seasonal prophylaxis, and strategies to prevent primary infection and relapses from *P vivax* malaria.

Evidence Acquisition Comprehensive search of scientific publications including MEDLINE via both OVID and PubMed for relevant studies and articles with a cutoff date of July 2006, using the search terms *long-term travel and malaria prevention*, *long-term malaria chemoprophylaxis*, and *insect repellent and malaria*. Additional references were obtained from searching the bibliographies of the selected articles, from dissertations, and from the proceedings of relevant conferences on travel medicine. There were no language restrictions.

Evidence Synthesis Long-term travelers have a higher risk of malaria than short-term travelers. Long-term travelers underuse personal protective measures and adhere poorly to continuous chemoprophylaxis regimens. A number of strategies are used during long-term stays: discontinuation of chemoprophylaxis after the initial period, sequential regimens with different medications for chemoprophylaxis, stand-by emergency self-treatment, and seasonal chemoprophylaxis targeting high-incidence periods or locations. All strategies have advantages and drawbacks. Counterfeit drugs sold in countries endemic for malaria pose serious concern for long-term travelers who purchase their medications overseas. Vivax malaria causes significant illness in travelers, but relapses of vivax malaria are not prevented with the current first-line chemoprophylaxis regimens. Consensus guidelines are needed for prevention of malaria in long-term travelers.

Conclusions Prevention of malaria in long-term travelers is a complex issue and requires expert advice from travel medicine specialists. Recommendations for prevention of malaria in long-term travelers must be individualized.

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nals for relevant reports over the past decade on malaria in travelers: *American Journal of Tropical Medicine and Hygiene*, *Annals of Internal Medicine*, *BMJ*, *Bulletin of the World Health Organization*, *Clinical Infectious Diseases*, *Emerging Infectious Diseases*, *JAMA*, *Journal of Infectious Diseases*, *Journal of Travel Medicine*, *Lancet*, *Lancet Infectious Diseases*, *Morbidity and Mortality Weekly Reports*, *New England Journal of Medicine*, *South-*

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east Asian Journal of Tropical Medicine and Public Health, Transactions of the Royal Society of Tropical Medicine, and Tropical Medicine and International Health. We placed emphasis on the more recent reports, especially systematic reviews, randomized controlled trials, and analyses of travelers' databases. All 3 authors performed the searches and added supplemental references; there were no disagreements.

EVIDENCE SYNTHESIS

Who Are Long-term Travelers?

In the GeoSentinel database (<http://istm.org/geosentinel/main.html>), 16% of patients with malaria had traveled for longer than 6 months.² For the purpose of our discussion, we defined *nonimmune travelers* as persons who reside in areas without malaria and who therefore do not have immunity to malaria parasites (although even residence in an endemic area does not result in fully protective immunity) and defined *long-term travelers* as nonimmune travelers visiting endemic areas for longer than 6 months. This is consistent with UK guidelines on the prevention of malaria in long-term travelers.³ However, many travelers visiting a destination for periods of less than 6 months will confront similar issues. Examples of long-term travelers include diplomats, students, missionaries, Peace Corps Volunteers, military personnel, teachers, field researchers, corporate employees, backpackers, and travelers who have frequent transient stays in malaria-endemic countries, such as airline crews.

Risk of Malaria in Long-term Travelers

An estimated 30 000 cases of malaria, 10 000 of them reported, are imported annually to nonendemic industrialized countries.^{4,5} The risk of malaria varies widely by geographic region. Between 1985 and 1988, the incidence of malaria in European travelers using no chemoprophylaxis was 15.2/1000 travelers per month in East Africa, and 24.2/1000 travelers per month in West Africa.⁶ Investigators using *Plasmodium falciparum* circumsporozoite an-

Table 1. Summary of Malaria Risk for Various Groups of Long-term Travelers*

Source	Type of Traveler	Malaria Risk
Blanke, ¹⁰ 2003	Expatriates in Morogoro, Tanzania, language school	4-Fold higher in nonimmune expatriates who used no chemoprophylaxis relative to those who used chemoprophylaxis
Leutscher and Bagley, ¹¹ 2003	Peace Corps Volunteers in Madagascar	15.9% of Peace Corps Volunteers reported malaria, or 8 per 100 Peace Corps Volunteers per year
Ross and Hodge, ⁹ 2000	Expatriates working for mining company sites in Africa	82% of expatriate workers in Zambia had diagnosis of malaria
Adera et al, ¹² 1995	US embassy personnel in Kampala, Uganda	Relative risk was 7.9 for those staying >2 y compared with <1 y; 10-fold increase in those using no chemoprophylaxis vs those taking mefloquine, doxycycline, or chloroquine-proguanil
Peppiatt and Byass, ¹³ 1991	Missionaries on leave to the United Kingdom	87.3 per 1000 persons per year; malaria was the most common illness, and risk was highest in West Africa
Phillips-Howard et al, ¹⁴ 1990	Returning British travelers	Relative risk in West Africa was 80.3 for a stay of 6-12 mo vs a 1-wk stay
Lange et al, ¹⁵ 1987	American mission boards	Malaria was the most common nontrivial medical problem; sub-Saharan Africa was region with highest risk
McLarty et al, ¹⁶ 1984	Urban expatriates in Dar es Salaam, Tanzania	37.1% reported history of infection with malaria ⁴

*Data may be inaccurate because of lack of good laboratory facilities in many areas, often leading to overdiagnosis of malaria.

tibody titers as a measure of malaria exposure found large variation in the proportion of seropositive travelers depending on the area visited: West Africa (22.2%), East Africa (21.8%), and southern Africa (15.4%), in contrast to Central America (4.2%), Southeast Asia (3.4%), East Asia (3.3%), South America (2.4%), and the Indian subcontinent (2.2%).⁷ Recent analyses of traveler databases have found the highest risk of acquiring malaria in Africa and Oceania, an intermediate risk in South Asia, and a lower risk in Central America, Southeast Asia, and South America.^{2,8} Long-term travelers, particularly occupational travelers such as miners, are at an even higher risk. In Zambia, 82% of expatriates working for a multinational mining company allegedly had malaria.⁹

TABLE 1 summarizes studies that assessed malaria risk in long-term travelers.⁹⁻¹⁶ Most were observational studies or surveys and may include overdiagnosis of malaria, which occurs commonly in malaria-endemic regions (often resource-poor settings).¹⁷⁻¹⁹ Febrile illnesses may be presumed to be malaria and treated without confirmatory blood

smears; blood smears, if performed, may be incorrectly read as positive for plasmodial parasites. In addition, blood smears in residents of endemic areas may be positive for malaria parasites even when malaria is not causing the illness. Nonetheless, these studies document that malaria is a serious problem and illustrate an increasing trend in malaria according to the duration of stay. Additionally, medical treatment or materials (eg, reused needles, syringes, blood transfusions) pose a risk of transmitting human immunodeficiency virus, hepatitis B virus, and other blood-borne infections, including malaria.²⁰

What options are available to reduce the risk of morbidity and mortality from malaria? Although no intervention is 100% effective, several approaches are available and can be used in combination. The following sections will review ways to minimize risk of infection and poor outcome if infection occurs. Any preparation should begin with education about basic elements of malaria transmission that will be tailored to the region where the person will be living and working. Key messages include seriousness of the in-

fection, protean manifestations of malaria, potential for rapid progression, need for rapid assessment, and possible onset many months after exposure, especially with vivax malaria.

Personal Protective Measures

The importance and effectiveness of personal protective measures should be emphasized with long-term travelers, including behaviors to minimize exposure to mosquitoes (eg, stay indoors from dusk to dawn, choose screened accommodations), barrier clothing, insecticide-impregnated bed nets, spraying of residence with insecticide, and application of effective insect repellent. Long-term travelers need concise instructions on clothing and bed-

net impregnation.²¹ “Knockdown” sprays (ie, those that kill mosquitoes on contact) can also be recommended, and the concept of “mosquito proofing” living accommodations (eg, maintaining drains, eliminating mosquito breeding sites, and installing screens) should be discussed in detail.²²

Insecticides (eg, deltamethrin and permethrin) are designed to kill mosquitoes and can be used effectively as knockdown sprays or in the impregnation of clothes and bed nets. Colombian soldiers who used permethrin-impregnated clothing had a reduced incidence of malaria (3%) compared with controls (14%).²³ Insecticide-treated bed nets are also highly effective in malaria prevention.²⁴

Repellents are substances applied to the skin to reduce the attractiveness of humans to mosquitoes and other arthropods. The US Environmental Protection Agency has registered a number of active ingredients as insect repellents: DEET (*N,N*-diethyl-*m*-toluamide [or *N,N*-diethyl-3-methylbenzamide]), picaridin (1-methyl-propyl 2-[2-hydroxyethyl]-1-piperidinecarboxylate [also known as KBR 3023 or Bayrepel]), PMD (*p*-menthane 3,8-diol [or oil of lemon eucalyptus]), MGK-326 (dipropyl isocinchomeronate), MGK-264 (*N*-octyl bicycloheptane dicarboximide), IR3535 (ethyl butylacetylaminopropionate), and oil of citronella.²⁵ DEET has the best evidence and longest history of use, and is considered the most reli-

Table 2. Main Results of Recent Comparative Studies on Insect Repellents

Source	Repellents Compared*	Type of Study	Location	<i>Anopheles</i> Species Tested	Efficacy and Duration of Protection
Fradin and Day, ²⁹ 2002	DEET (23.8%) vs other repellents	Arm-in-cage study	Indoors	None (study tested against <i>Aedes aegypti</i>)	DEET protected for 5 h; efficacy was best of those tested
Frances et al, ³⁰ 2002	Picaridin (9.3%† and 19.2%) vs DEET (20%, 33%, and 35%)	Field trial	Northern Queensland, Australia	<i>A farauti</i> ss <i>Laveran</i>	Picaridin (19.2%) is comparable to DEET (35%); nighttime use provided 95% protection for >7-9 h; picaridin (9.3%†) provided >95% protection for only 2 h
Badolo et al, ³¹ 2004	Picaridin (diluted in ethanol) vs DEET	Arm-in-cage study	Laboratory in Burkina Faso	<i>A gambiae</i> sl	Picaridin similar to DEET for <i>A gambiae</i> complex
Frances et al, ³² 2004	Picaridin (19.2%) vs DEET (20% and 35%)	Field trial	Northern Territory, Australia	<i>A meraukensis</i> Venhuis, <i>A bancroftii</i> Giles	Picaridin provided >95% protection against <i>Anopheles</i> mosquitoes for only 1 h, similar to DEET (35%); DEET (20% in ethanol) protected poorly against <i>Anopheles</i> mosquitoes
Costantini et al, ³³ 2004	Picaridin vs IR3535 and DEET	Field trial	Burkina Faso	<i>A gambiae</i> sl	Picaridin provided best protection for <i>A gambiae</i> complex after exposure of 10 h; picaridin lasted longer, has longer half life after application on skin than other 2 agents
Trigg, ³⁴ 1996	PMD vs DEET	Human-landing catches	Tanzania	<i>A gambiae</i> and <i>A funestus</i>	PMD and DEET protected for 6-7.75 h
Govere et al, ³⁵ 2000	PMD (0.574 g) vs DEET (15%) vs Bio-Skincare (BSC)‡	Arm-in-cage study	Indoors	<i>A arabiensis</i> patton	PMD and DEET provided 90%-100% protection for up to 5-6 h; BSC protected for up to 3-4 h
Moore et al, ³⁶ 2002	PMD (30%) vs DEET (15%)	Human-landing catches	Bolivia	<i>A darlingi</i>	PMD provided 97% protection for 4 h; DEET provided 85% protection
Trongtokit et al, ³⁷ 2005	PMD (10% and 20%), citronella (40%), DEET (50%)	Arm-in-cage or mosquito-proof room study	Indoors	<i>A stephensi</i>	PMD (20%) provided complete repellency for 7-8 h but PMD (10%) for only 30 min; citronella (40%) protected for 7 h; DEET (50%) protected for 30 h

*See “Personal Protective Measures” section for chemical and alternate names of repellents.

†The only product available in the United States contains low effective concentration.

‡A product containing oils of coconut, jojoba, rapeseed, and vitamin E.

able. Most repellents are water soluble and need to be reapplied frequently when profuse sweating occurs.

No systematic analyses address the safety of long-term use of repellents, though no reports of problems with long-term use have been published. DEET-containing repellents have been widely used since the 1950s, and toxicity is extremely rare and associated with inappropriate rather than prolonged duration of use.²⁶ Moreover, experience with the use of 20% DEET during the second and third trimesters of pregnancy in women on the Thai-Myanmar border with follow-up of infants through 1 year of age demonstrated no increase in adverse neurologic, gastrointestinal tract, or dermatologic effects.²⁷ More recently, DEET-containing products have been sanctioned for use in infants older than 2 months.^{25,28}

The activity of a repellent may not be the same against all species of mosquitoes or against other arthropods, such as ticks. Anopheline, *Aedes*, and *Culex* mosquitoes are important vectors of human pathogens, but only anopheline mosquitoes transmit malaria. One comparison showed that DEET-based products provided the longest protection against *Aedes* mosquito bites; higher concentrations lasted longer, and 23.8% DEET protected a mean of 5 hours.²⁹ Some recent studies have found picaridin, DEET, and PMD effective against *Anopheles* mosquitoes³⁰⁻³⁷ (TABLE 2).

Because picaridin has a longer half-life after application on skin, it may be particularly useful in areas with high vector densities.³³ However, the available products in the United States do not contain the optimal effective concentration and are not currently recommended for prevention of malaria. Long-term travelers also need to be aware of the biting habits of the local *Anopheles* populations, although this information is not readily available before travel. *Anopheles gambiae* bites mainly late at night, emphasizing the importance of impregnated bed nets in Africa, whereas *A. darlingi* (an important vector in the Amazon basin) bites earlier in the evening,

Table 3. Evidence Regarding Efficacy of Personal Protective Measures*

Source	Type of Report	Method	Effect
Keiser et al, ²² 2005	Systematic literature review	Environmental management	Environmental modification (to reduce vector habitats) and modification of human habitation reduced the risk ratio of malaria by 80%-88%†
Lengeler, ²⁴ 2004	Systematic review of randomized controlled trials	Insecticide-treated bed nets	Areas with stable malaria: treated bed nets reduced uncomplicated malaria incidence by 50% vs no nets and 39% vs untreated nets Areas with unstable malaria: treated nets reduced <i>Plasmodium falciparum</i> by 62% vs no nets and 43% vs untreated nets Protective efficacy of 45% for severe malaria, 13% for parasite prevalence, 29% for high parasitemia, 30% for splenomegaly
Soto et al, ²³ 1995	Double-blind, randomized study	Permethrin-impregnated clothing	Method reduced malaria incidence to 3% in Colombian soldiers (vs 14% in controls)
Durrheim and Govere, ⁴⁰ 2002	Observational study in endemic area	DEET	Application of 15% DEET to ankles and feet of villagers in Kruger National Park, South Africa, reduced bites from <i>Anopheles arabiensis</i> and restored malaria incidence to pre-epidemic levels
Govere et al, ³⁹ 2001	Human-bait study in open air	DEET	Application of 15% DEET to human ankles and feet reduced bites by <i>A. arabiensis</i> patton by 69%

*See "Personal Protective Measures" section for chemical names of DEET.

†These measures included installing drains and underground pipes; filling swamps, pits, pools, and ponds; modifying river boundaries to improve flow; clearing of undergrowth and mangroves; changing irrigation to intermittent systems; screening houses; closing eaves and ceilings.

suggesting that repellents would be pivotal in this area.^{36,38-40}

TABLE 3 summarizes evidence of benefit regarding personal protective measures.^{22-24,39,40} However, adherence to personal protective measures such as use of screened accommodations, repellents, insecticides, and bed nets by long-term travelers is suboptimal.⁴¹⁻⁴³ A study evaluating knowledge, attitudes, and practices of travelers found that only 2% of tourists and 3.8% of business travelers adhere to an effective combination of personal protection measures.⁴⁴ Finally, misconceptions about approaches, such as thiamine (vitamin B₁), garlic, or ultrasound devices and electronic buzzers, that do not work.⁴⁵

Malaria Chemoprophylaxis

Although personal protective measures and environmental and behavioral modifications can reduce the risk of exposure to infective mosquitoes, these interventions cannot eliminate

risk of infection. In combination with these measures, chemoprophylaxis can further reduce the risk of poor outcome if a person is bitten by infective mosquitoes.⁴⁶ Most chemoprophylactic regimens provide about 75% to 95% protection, even if taken correctly,⁴⁷ and no chemoprophylactic regimen is 100% effective. Long-term travelers may plan pregnancy while in malarious areas, but malaria during pregnancy is associated with severe consequences to both mother and fetus, and special considerations are needed because some chemoprophylactic drugs are contraindicated during pregnancy (TABLE 4).

Restrictions on the Duration of Use of Chemoprophylaxis

In general, the drugs used for chemoprophylaxis have been used widely for many years, though primarily in short-term travelers, and their adverse effects are well known. Concerns arise when these drugs are considered for

prolonged use. The licensing restrictions probably contributed to concerns about long-term use of some chemoprophylactic medications. Table 4 summarizes these restrictions, the clinical data on long-term use, and the duration of use approved by the UK Advisory Committee on Malaria Prevention.^{3,48-51}

Safety of Malaria Chemoprophylaxis for Long-term Travel

Chloroquine has been used in a continuous manner for years by travelers as well as patients with rheumatologic disorders. Retinal toxicity is of concern when a 100-g cumulative dose of chloroquine base is reached, usually after 5 to 6 years of weekly dosing. The UK Advisory Committee on Malaria Prevention recommends ophthalmologic examination every 6 to 12 months after 5 to 6 years of use.³ Similar caution and screening are recommended for hydroxychloroquine.

For areas with chloroquine-resistant malaria, mefloquine is considered a convenient option for long-term chemoprophylaxis due to its simple dosage schedule (once weekly), wide experi-

ence (especially from Peace Corps studies in Africa), pharmacokinetic data indicating that drug accumulation does not occur after long-term intake, and good tolerability during prolonged use.^{48,52,53}

Adverse effects of mefloquine have caused concern. The incidence of serious adverse effects associated with mefloquine was previously estimated to be 1 in 6000 to 1 in 10 600.^{54,55} A double-blind, placebo-controlled study of airline pilots using a flight simulator found that mefloquine was associated with nonserious sleep-related adverse effects but no significant adverse influence on performance.⁵⁶ Another double-blind study comparing the tolerability of mefloquine, chloroquine-proguanil, doxycycline, and atovaquone-proguanil as chemoprophylactic regimens showed relatively poor tolerability for all regimens, with more than 80% of participants reporting at least 1 adverse event; severe adverse events (ie, those requiring medical attention) were reported in 12% of mefloquine users, compared with 11% with chloroquine-proguanil, 6% with doxycycline, and 7% with atovaquone-proguanil.⁵⁷ In

contrast, mefloquine use among US service members from 2002-2004 was not associated with severe health effects.⁵⁸ Mefloquine was well tolerated when used for more than 3 months in Italian soldiers in Somalia and Mozambique⁵⁹ as well as in Peace Corps Volunteers, where it was used for up to 2.5 years.⁴⁸ Only 0.3% of Dutch marines who used mefloquine for 6 months reported adverse effects requiring medical attention.⁶⁰ Mefloquine adverse events tend to occur early in prophylaxis; if users initially tolerate mefloquine, they are unlikely to have late-onset adverse events.⁴⁸

Postmarketing surveillance of the use of atovaquone-proguanil for up to 34 weeks has found some association with gastrointestinal tract adverse events (diarrhea, abdominal pain, mouth ulcers, nausea, vomiting) and neuropsychiatric adverse events (dizziness, insomnia, vivid dreams) in 10% and 8.5% of users, respectively, but only 1% discontinuation (due to diarrhea).⁴⁹ Australian soldiers deployed to Somalia for 4 months and to Cambodia for 12 months used doxycycline; adverse events led to a medication change in

Table 4. Data on Duration of Use of Malaria Chemoprophylactic Drugs

Source	Drug (Proprietary Name)	Licensed Duration in United States	Restrictions on Duration of Use Elsewhere	Longest Published Clinical Use	Safety in Pregnancy ⁴³	UK ACMP Recommendations ³
Lobel et al, ⁴⁸ 1993	Chloroquine phosphate (Aralen) or hydroxychloroquine sulfate (Plaquenil)	No limit	No limit, but caution in use >5 y	2-2.5 y in Peace Corps Volunteers	Yes	No limit, but retinal toxicity a possible concern when cumulative dose exceeds 100 g; ophthalmologic examination every 6-12 mo after taking chloroquine for >5-6 y
Lobel et al, ⁴⁸ 1993	Mefloquine (Lariam)	No limit	No limit	2-2.5 y in Peace Corps Volunteers	Yes	Up to 3 y
Overbosch, ⁴⁹ 2003	Atovaquone-proguanil (Malarone)	No limit	Maximum of 28 d-3 mo (most European countries)	34 wk postmarketing surveillance	Unknown, avoid	At least up to 3 mo, possibly up to ≥6 mo
Shanks et al, ⁵⁰ 1995	Doxycycline (Vibramycin, Doryx, and others)	4 mo	2 y for acne treatment (United Kingdom)	12 mo in Australian Defense Force to Cambodia	Contraindicated	At least up to 2 y
Fryauff et al, ⁵¹ 1995	(Primaquine)*	No limit	No limit	52 wk in nonimmune Javanese transmigrants to Papua New Guinea	Contraindicated	No specific recommendation on duration

*Must screen for G6PD deficiency first.

1.7% (Somalia) and 0.6% (Cambodia).⁵⁰ A series of 35 patients with Q-fever endocarditis treated with doxycycline, 100 mg twice daily, for up to several years reported photosensitivity in all patients but irreversible skin pigmentation in only 1.⁶¹

Primaquine (which can be used only in persons who do not have glucose-6-phosphate dehydrogenase [G6PD] deficiency), 30 mg daily, was well tolerated for up to 52 weeks as primary prophylaxis for *P falciparum* and *P vivax* in clinical trials in Javanese transmigrants.^{51,62}

Adherence With Chemoprophylaxis During Long-term Intake

Adherence to chemoprophylaxis in long-term travelers has been poor.^{16,43,48,63-67} The use of malaria prophylaxis in missionaries was dismal, ranging from 19% to 62%, even counting persons who missed doses.^{43,65} Only 38% of expatriate mine workers in Zambia used any chemoprophylaxis; of these, only half took the medication year around.⁶⁶ Among expatriate workers at a construction site in Ghana, only 11% continued to take malaria prophylaxis for more than 7 months; half stopped their antimalarial agent or changed to a new agent based on medical advice, adverse effects, a perceived low risk of malaria, or advice of local colleagues.⁶⁷ Commonly cited reasons for poor adherence include fear of long-term adverse effects, adverse events from medication, conflicting advice, and complicated regimens or daily medications. Developing malaria while taking chemoprophylactic drugs (ie, "breakthrough" malaria) or having febrile illnesses misdiagnosed as malaria also reduce confidence in chemoprophylaxis.³

Different approaches have evolved (TABLE 5). These include continuing the medication beyond licensed durations, using different chemoprophylactic regimens sequentially, using a regimen such as chloroquine-proguanil that has no time limit but has suboptimal efficacy, and discontinuing chemoprophylaxis in favor of

Table 5. Advantages and Disadvantages of Malaria Prevention Approaches in Long-term Travelers

Approach	Advantages	Disadvantages
Personal protective measures	Effective with minimal toxicity	Cumbersome during a long trip or stay Traveler may not be reliable in application Must be used consistently
Continuous chemoprophylaxis	Most reliable method for medication in high-risk regions	Adverse events from medication Expensive Poor adherence
Seasonal prophylaxis	Best for areas with clear seasons of transmission, knowledgeable and responsible travelers Less medication	Must have knowledge of local malaria epidemiology Weather pattern shifts can lead to variation in transmission of malaria Requires detailed instructions Need to also carry SBET Access to good medical care required
Initial prophylaxis followed by SBET	Best for knowledgeable and responsible travelers with long stays in 1 location Traveler has control Less medication	Traveler may not arrange medical care Traveler may not seek evaluation appropriately
SBET	Best for knowledgeable and responsible travelers Traveler has control Less medication Positive risk-benefit analysis for long-term travelers in low-risk areas May be life-saving in certain circumstances Low cost	Misuse/overuse of medication Errors can occur regarding medication dose or schedule Traveler may not seek medical evaluation for febrile illness Weather pattern shifts can lead to variation in transmission of malaria Requires detailed instructions
Combination of seasonal or initial prophylaxis with SBET	Best for knowledgeable and responsible travelers	Need detailed instructions Other problems as above

Abbreviation: SBET, stand-by emergency treatment.

establishing local medical care and stand-by treatment. "Mixing and matching" of antimalarial agents can lead to gaps in protection. This can occur when an individual shifts from one antimalarial agent to a different one because of drug unavailability or adverse reactions or because of travel to regions where parasites have different resistance patterns.

Stand-by Emergency Self-treatment

As defined by the World Health Organization, "stand-by emergency treatment (SBET) is the use of anti-malarial drugs carried by the traveler for self-administration when malaria is suspected and prompt medical attention is unavailable within 24 hours of onset of symptoms."⁴

The World Health Organization initially recommended SBET for short-

stay travelers based on data that suggested that 22% of malaria infections had been treated abroad and at a time when chloroquine resistance emerged and mefloquine had not yet been approved by the US Food and Drug Administration.⁶⁸ Stand-by treatment was recommended for travelers to areas with low malaria transmission but no reliable diagnostic and therapeutic facilities (parts of Southeast Asia) and areas at high risk for *P falciparum* where the prescribed chemoprophylactic drug, chloroquine, at that time was not considered to be highly effective (parts of East and Central Africa).⁶⁸ A switch from continuous chemoprophylaxis to SBET in Swiss airline crews reduced by two thirds the number of malaria tablets used from 1984 to 1988, and there were no malaria fatalities.⁴¹ Since 1988, Swiss malaria guidelines for travelers have

recommended SBET for travelers to low-risk malaria areas.⁶⁹

Much debate regarding SBET ensued. Assessment of Swiss and German travelers who used SBET found 4- to 10-fold overuse.^{70,71} The drugs can have adverse effects and can be inappropriately used for illnesses that require other treatment. Further study of Swiss travelers who were prescribed SBET found that one third of patients ill with malaria-like symptoms did not seek medical attention as advised.⁷⁰ Adherence to SBET guidelines is a recognized problem with the SBET strategy, and travelers need concise oral and written instructions and personalized dosage schedules for family members.⁷¹ Errors associated with SBET use include changing chemoprophylaxis, ie, the tendency to replace chemoprophylaxis with SBET (11%); lack of confirmation of diagnosis after initiating SBET (25%); lack of medical evaluation (25%); and mistakes with medication (88%).⁷¹ Self-diagnosis of malaria is unlikely to be correct.^{70,71} Use of SBET can lead to delayed diagnosis of other serious conditions.⁷²

Currently, SBET alone is recommended for Swiss and German travelers to low-risk areas of Asia and Central and South America, while

chemoprophylaxis remains the best strategy for travelers going to areas with high *P falciparum* transmission, such as sub-Saharan Africa and Papua New Guinea.⁷³ Recently some European experts have also adapted the SBET strategy for travelers to India, because new data on imported malaria from the Indian subcontinent showed a very low risk of infection⁷⁴ and suggested that most imported infections are late-onset *P vivax* infections. In many European countries, atovaquone-proguanil or a fixed combination of artemether-lumefantrine (not available in the United States) are recommended as ideal SBET. Chloroquine can be recommended as SBET only in Central America due to widespread resistance elsewhere. Mefloquine can also be used as a reasonably priced SBET but has been associated with considerable adverse events at therapeutic doses.⁷⁵ Quinine remains an option for pregnant women but has a complicated dosage schedule. Two older medications that were originally recommended for SBET are now contraindicated: sulfadoxine-pyrimethamine (due to fatal adverse events)⁷⁶ and halofantrine (associated with sudden death in travelers due to fatal arrhythmias)⁷⁷ (TABLE 6).

The US Centers for Disease Control and Prevention currently does not recommend SBET alone for travel to low-risk areas but does recommend atovaquone-proguanil for SBET, which applies to high-risk areas where SBET should be considered in addition to chemoprophylaxis in the event a traveler needs to self-treat.⁴⁶ Because of the concern for resistance and additive toxicity, the medication used for SBET should differ from what the traveler uses for chemoprophylaxis.

Use of Rapid Diagnostic Tests

A major drawback of SBET is the difficulty encountered by travelers in correctly diagnosing a malaria infection. In 1994 it was suggested that trained travelers could use rapid dipstick malaria tests,⁷⁰ and thereafter self-testing has been evaluated in healthy and febrile travelers.⁷⁸⁻⁸⁰ Except for one study of UK travelers⁸¹ in which 91% of participants could successfully perform and interpret the test, the approach has been hampered by technical difficulties on the part of travelers and also by the issues of false-positive and false-negative results. Components of the rapid tests are likely to deteriorate during long-term storage in tropical climates.⁸² These tests currently are not

Table 6. Medications Recommended as Stand-by Emergency Self-treatment (SBET)

Medication (Proprietary Name)*	Adult Dosage	Advantages	Disadvantages
Artemether-lumefantrine (20 mg/120 mg) (Riamet; Co-Artem)	80 mg/480 mg, then 80 mg/480 mg in 8 h, then 80 mg/480 mg every 12 h for 2 d (24 tablets over 3 d)	Effective against multiresistant <i>Plasmodium falciparum</i> Rapid parasite and fever clearance Good safety/tolerability profile for children >10 kg	Not available in the United States Short shelf life (<2 y) Not for pregnant women Needs to be taken with food
Atovaquone-proguanil (250 mg/100 mg) (Malarone)	1000 mg/400 mg daily for 3 d (12 tablets over 3 d)	Effective against multiresistant <i>P falciparum</i> Good safety/tolerability profile Pediatric dosing available for children >11 kg	Potential for resistance development Not for pregnant women Interaction with paracetamol and metoclopramide
Mefloquine (Lariam, 250-mg base; Mephaquin, 250-mg base)	750-mg base, then 500 mg in 12 h (5 tablets in 1 d)	Inexpensive Wide experience Effective against all Plasmodial species Can be used for children >5 kg Can be used in second and third trimesters of pregnancy	Increasing <i>P falciparum</i> resistance Neurotoxicity increases at treatment doses (1:216) ⁷¹ Negative reports in media
Chloroquine (Chlorochin, 150-mg base; Nivaquin, 100-mg base)	600-mg base, then 300 mg in 6 h, 300 mg daily for 2 d (10 tablets over 3 d)	Inexpensive Can be used for children >5 kg Can be used in pregnancy	Widespread resistance Can only be recommended for travelers to Central America and the Caribbean

*Halofantrine (Halfan) and sulfadoxine-pyrimethamine (Fansidar) are no longer recommended as SBET.

available to travelers in the United States.

Counterfeit Drugs

Counterfeit drugs, including antimalarial drugs, are widely distributed, especially in Asia. Long-term travelers are likely to purchase their drugs in the country of temporary residence unless they return frequently to their home country or can arrange shipment or delivery of drugs.⁸³⁻⁸⁶ Problems with counterfeit drugs include incorrect amount of active ingredient, toxic or allergenic additions to medication, and formulations that may have different pharmacokinetic properties. Long-term travelers must understand these issues and obtain safe, real, and effective medications. A recent report identified at least 12 different counterfeit artesunate products in circulation in Southeast Asia.⁸⁵

Seasonal Prophylaxis

No national or international guidelines recommend using chemoprophylaxis only periodically for long-term travel to areas of malaria risk. However, some long-term travelers prefer this approach over continuous chemoprophylaxis.^{67,87} However, if travelers take chemoprophylaxis only in seasons or locations with higher transmission seasons, they also need access to reliable medical care and SBET. Despite the lack of formal proposal or assessment of seasonal malaria prophylaxis in long-term travelers, the practice may be common among expatriate workers in some locations. Among the expatriate workers at a construction site in Ghana, 6.3% varied their use of antimalarial agents according to the time of the year.⁶⁷

Seasonal chemoprophylaxis for long-term travelers poses a number of problems. It requires knowledge of the local malaria epidemiology, but such data may be unavailable. Travelers using seasonal prophylaxis (eg, only during a high-transmission season, typically the rainy season) risk developing symptomatic malaria when they discontinue suppressive chemoprophylaxis. In contrast to residents in malaria-

endemic areas who develop partial immunity over many years, long-term travelers are not immune and are at risk for severe and complicated malaria. Some countries, such as Botswana, Namibia, and South Africa have clearly defined high- vs low-transmission seasons,²¹ but unusual weather changes can alter the transmission pattern. Therefore, seasonal malaria prophylaxis should be considered an alternative strategy only for some long-term travelers who clearly understand these complex issues. All long-term travelers should identify medical facilities (and types of services offered) that are available to them locally and regionally.

Vivax Malaria in Long-term Travelers

The primary goal of prophylaxis is prevention of severe morbidity and deaths from malaria. Most deaths are from falciparum malaria; vivax malaria, which can be severe, is rarely lethal. However, vivax malaria can have a long latency and present many months after a trip, at a time when the traveler may not recall the exposure. The malaria chemoprophylactic regimens commonly used (chloroquine, doxycycline, mefloquine, atovaquone-proguanil) prevent the blood-stage infection but do not prevent relapses of vivax malaria because they do not eliminate the liver-stage parasites (hypnozoites). Falciparum and vivax are the dominant plasmodial parasites in all malarious areas, though the intensity of transmission and relative proportion contributed by each species varies by geographic area and may change over time. In most countries in sub-Saharan Africa, falciparum causes 85% or more of the malaria cases, yet absolute risk of vivax malaria may be higher than in countries in which vivax malaria accounts for all cases but the level of transmission is low. Approximately one third of vivax malaria cases imported to Europe from 1999 to 2003 and reported to TropNetEurop (<http://www.tropnet.net>) followed exposures in sub-Saharan Africa.⁸⁸ Although severe complications were rare, 60% of the patients were hospitalized.

Vivax malaria accounts for one quarter to more than one half of malaria cases in travelers in some series^{2,89-91} and varies depending on the predominant destination. High attack rates of vivax malaria have been reported in short-term travelers after intense exposures, eg, a 50% infection rate was reported among Israeli travelers (taking mefloquine prophylaxis) to Ethiopia.⁸⁹ Additionally, more than 60% to 80% of travelers with vivax malaria present at least 2 months after departure from the risk area (late onset), when clinical suspicion for malaria may be low.⁹⁰

In recent years, about one quarter of reported malaria cases in the United States (in US and foreign civilians and US military personnel) were due to *P vivax* (among cases where species was identified); an additional 2.6% to 3.6% were attributed to *P ovale*.⁹²⁻⁹⁴ Countries and regions contributing the largest numbers of vivax malaria cases were (by order of contribution, starting with the region contributing the most cases): Asia (India and Pakistan most often), Africa, Central America and the Caribbean, Mexico, Oceania (primarily Papua New Guinea), and South America. Among the cases of vivax malaria reported to the GeoSentinel database, exposures in Africa accounted for 29.5%; Asia, 27%; Oceania/the Pacific, 19.5%; and the Americas, 16.8%.⁹¹ More detailed global distribution of *P vivax* is described elsewhere.^{21,95}

Vivax and ovale are the 2 plasmodial species that have dormant forms, ie, hypnozoites, that remain in the liver and can later enter the bloodstream to cause clinical relapses. Korean War soldiers treated with chloroquine for vivax malaria experienced fewer relapses after the addition of primaquine, an 8-aminoquinoline; this was called radical cure.^{96,97} Use of drugs to eradicate incubating liver hypnozoites, also called presumptive antirelapse treatment or terminal prophylaxis, refers to the administration of primaquine to asymptomatic persons after their departure from an area where exposure to *P vivax* may have occurred and is usually administered during the last 2 weeks of malaria chemoprophylaxis.

The recommended primaquine dose for antirelapse treatment was recently increased from 15 mg to 30 mg daily for 14 days^{46,98} because of high failure rates with the lower dose.⁹⁹ Relapses have been more common in travelers who have visited Papua New Guinea or eastern Indonesia, where the vivax strain (Chesson) appears to be more resistant to drugs.⁹¹ The timing and combination with other antimalarial agents appear to be important. A higher cure

rate occurred in treating the Chesson strain of *P vivax* with concurrent administration of primaquine with quinine or chloroquine rather than sequential administration of quinine followed by primaquine.¹⁰⁰

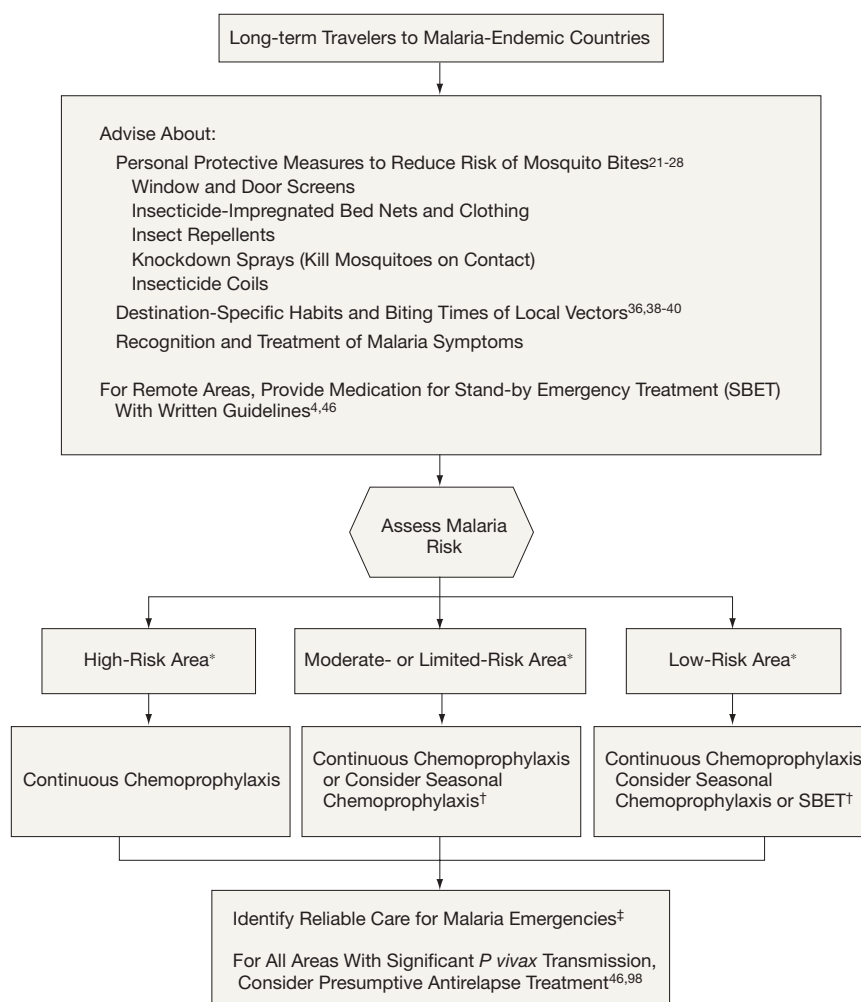
For travelers who may have had significant exposure to *P vivax* (eg, long-term travelers to Papua New Guinea and other areas with substantial vivax transmission), primaquine, 30 mg daily, is currently recommended as antire-

lapse treatment to be given near the end of the course of chemoprophylaxis. Although data suggest that the combination of primaquine with chloroquine or quinine eradicates hypnozoites, so far there is no evidence that primaquine alone is effective in preventing relapse. Primaquine can generally be started after the traveler has returned home (and is still completing chemoprophylaxis), though travelers need to be advised before departure that they should schedule an appointment on return. Screening for G6PD deficiency is essential before administering primaquine. Some data suggest that a weekly dose of primaquine can be considered (for radical cure, not antirelapse treatment) in patients with mild G6PD (usually the A-variant) deficiency.⁹⁸ Whether or not returned travelers receive antirelapse treatment, they should be informed of the potential for late relapse and the need to seek medical attention. They should inform their clinicians about their durations of exposures in malarious areas.

CONCLUSIONS

Long-term travelers to malaria-endemic areas face risk of death, morbidity, and reduced productivity because of malaria. General guidelines are desirable, but recommendations for malaria prevention in long-term travelers must be individualized and should be provided by travel medicine specialists (Table 5). Personal protective measures are paramount. Identification of reliable medical facilities at destinations is crucial for long-term travelers regardless of their malaria prevention strategies, and a number of resources are available to aid in this process (eg, the International Society of Travel Medicine Web site [<http://www.istm.org>] and the International Association of Medical Assistance to Travellers Web site [<http://www.iamat.org>]). Data on safety of chemoprophylaxis drugs show reasonable clinical support for long-term use, particularly for mefloquine. Many long-term travelers use a combination of strategies (FIGURE). Factors and decisions influencing the choice of ap-

Figure. Algorithm for Malaria Prevention in Long-term Travelers



The algorithm represents the authors' opinions and not the opinion of official guidelines. The US Centers for Disease Control and Prevention (CDC) recommends consideration of SBET in addition to continuous chemoprophylaxis for travel to areas where self-treatment may be necessary and for travelers taking suboptimal chemoprophylaxis.

*Categories of malaria risk are defined based on world regions and country-specific risk levels.^{2,7,8,21,94}

†The CDC currently does not recommend SBET alone or seasonal chemoprophylaxis for any malarious areas.

‡Rapid diagnostic tests for malaria could become an attractive option in occasional circumstances if technical problems are overcome.⁷⁸⁻⁸²

proaches include intensity of transmission, predominant parasite, duration of stay, resistance pattern, host factors, access to care, personal preference, economics, other health issues, and G6PD status. More data are needed to adequately recommend alternatives to continuous chemoprophylaxis. All travelers should be advised to carry or arrange adequate supplies of antimalarial agents, because counterfeit drugs are rampant in developing countries. Long-term travelers should also consider evacuation insurance for medical emergencies. The components of rapid dipstick tests are likely to deteriorate under tropical conditions, but such tests may be considered for certain travelers at remote locations. Presumptive antirelapse therapy should be considered for long-term travelers who have been intensively exposed to *P. vivax*. Because inconsistent recommendations undermine the adherence to any preventive strategy, national and international experts should strive toward consensus on guidelines for malaria prevention in long-term travelers.

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